AMENDMENTS TO THE DRAWINGS:

Please replace sheet 8 of the Figures (labeled "Fig. 3C") with the attached replacement sheet "Fig. 3C."

As shown on the attached annotated version of the amended Figure 3C, the sequence identifiers listed to the right of the amino acid sequences shown in the figure have been changed. Specifically, the sequence numbers 54-57 have been replaced with numbers 8-11, respectively. The new numbers correspond to the new sequence identifiers for the depicted amino acid sequences as set forth in the second substitute sequence listing submitted herewith.

Applicants submit that the amendment of the sequence identifiers in Figure 3C does not constitute new matter.

Attachments: Replacement Sheet
Annotated Sheet Showing Changes

REMARKS

The specification, claims, Sequence Listing, and Figures have been amended as follows.

Amendments to the specification

The priority information at page 1 has been updated and a grammatical error has been corrected.

The description of Figure 3 at page 13 of the specification has been amended to correct the amino acid sequence of the tryptic peptide described at line 16. Specifically, a glycine (G) residue has been inserted at the amino terminus of the peptide. Support for this amendment is found in Figure 3A as originally filed.

Appropriate sequence identifiers have been added to the specification and figures where amino acid and/or nucleotide sequences are disclosed. Specifically, the description of Figure 3C on page 13 has been amended to insert the sequence identifiers depicted in the amended Figure 3C submitted herewith. In addition, for clarity, the peptide sequences to which the sequence identifiers correspond have been listed. Support for the inserted amino acid sequences is found in Figure 3C as originally filed. Applicants note that sequence identifiers were previously added to the specification for the amino acid sequences depicted at pages 13 and 59 of the specification (see Applicants' Supplemental Amendment filed May 25, 2004).

The description of Figure 6B on page 13 has been amended to correct a typographical error in the word "α2M" which should read "α2MR" for "α2M *receptor*." Support for this amendment is found in the original description of Figure 6B which indicates that the amino acid sequence depicted in the figure is that of the α2M *receptor*, not the receptor ligand, α2M. Specifically, the original description of Figure 6B states that ". . . an 80 kDa, gp96-interacting fragment *of the receptor* [is] highlighted in bold." Further support is found in the specification at page 63, lines 1-2, which states that "[t]he 80 kDa protein shown to bind gp96 is clearly an amino terminal degradation product of the α subunit of the α2M receptor." Applicants further note that the amino acid sequence depicted in Figure 6B is the same as that which is predicted from the α2M receptor cDNA shown in Figure 6A.

The description of Figure 7 has been amended to correspond with the information actually depicted in that figure. Specifically, the description of Figure 7A now recites the *nucleotide* sequence of α2M because panel A of Figure 7 depicts the nucleotide sequence of

α2M along with the predicted amino acid sequence which is shown below the nucleotide sequence. Likewise, Figure 7B now recites the *amino acid* sequence of α2M because panel B of Figure 7 depicts that amino acid sequence. In addition, the word "underlined" has been replaced with the word "highlighted" in the description of panel B because the figure shows this region as highlighted, not underlined. Applicants note that the amino acid sequence in Figure 7B differs from that of the translated amino acid sequence in Figure 7A because Figure 7B depicts the sequence of the mature human α2M protein following cleavage of the N-terminal 23 amino acid signal sequence.

Finally, the specification has been amended to delete any embedded hyperlinks and/or other forms of browser-executable code.

Applicants believe that no new matter has been added by these amendments to the specification.

Amendments to the claims

Claims 1, 7-9, 40, and 42-50 were pending in this application before entry of the amendments made herein. Applicants have amended claims 8, 9, 40, 43, 44, 46, 47, and 50 to clarify the claimed invention, and have added new claims 51-64. Specifically, claims 8, 9 and 47 have been amended to recite that the molecular complexes are at least 65% noncovalent complexes. Support for this amendment can be found in the specification at, *inter alia*, page 8, lines 29-32.

Claims 43, 44 and 47 have also been amended to add the proviso that the infectious agent is other than hepatitis type B virus, and claim 46 has been amended to delete the recitation of "hepatitis type B virus." Support for the amendment to claims 43, 44, 46, and 47 is found in the specification as originally filed. Support for the proposition that claims can be properly amended to exclude one or more species of a genus when the specification provides a generic disclosure of the genus and numerous species within the genus, including the species being excluded from the scope of the claim, can be found in *In re Johnson*, 558 F.2d, 1008, 1019 (*see also* § 2173.05(i) of the Manual of Patent Examining Procedure, Eighth Edition, Revision 3, August 2005, at page 2100-223). Here, the specification provides a generic disclosure of intracellular pathogens which cause an infectious disease, and numerous species therein, including hepatitis type B virus (see page 52, lines 8-21). According to *Johnson*, the claims can be properly amended to exclude hepatitis type B virus as an infectious agent.

The dependency of claim 50 has been amended, and new claims 51-53 have been

added to replace the dependencies deleted from claim 50. Support for new claims 50-53 and 63-64 can be found in the specification at, *inter alia*, page 8, lines 23-24. Support for new claims 54-60 can be found in the specification at, *inter alia*, page 8, lines 3-4 and 13-18; and page 8, line 27, to page 9, line 5. Support for new claims 61 and 62 can be found in the specification at, *inter alia*, page 8, lines 13-18.

Applicants believe that no new matter has been added by these amendments to the claims Upon entry of the present amendments, claims 1, 7-9, 40, and 42-64 will be pending in the present application.

Amendments to the Sequence Listing

Applicants submit herewith a substitute sequence listing which contains the following additions and deletions relative to the previous sequence listing submitted on May 25, 2004.

The May 25, 2004 sequence listing contained "empty" sequence identifiers numbered 8 to 54 which did not contain any sequence information. These empty identifiers have been deleted, and subsequent identifiers renumbered.

SEQ ID NO: 5 has been amended to conform with the description of Figure 7 and the sequence information in that figure. Specifically, the description of Figure 7 as originally filed indicates that SEQ ID NO: 5 is an amino acid sequence of 138 residues representing the receptor binding domain ("RBD") of α2M and shown in Figure 7. However, the SEQ ID NO: 5 added in Applicants' May 25, 2004 sequence listing does not correspond to the 138 amino acids of the RBD depicted in Figure 7B. SEQ ID NO: 5 has been amended to conform with the amino acid sequence highlighted in Figure 7B. Thus, new SEQ ID NO: 5 is identical to the highlighted portion of the sequence depicted in Figure 7B. Support for the amendment to SEQ ID NO: 5 is found in the description of Figure 7 at page 13, lines 34-36 and in Figure 7 as originally filed.

SEQ ID NO: 6 has been amended to conform with the sequence depicted in Figure 3A.

SEQ ID NO: 8 has been added. SEQ ID NO: 8 corresponds to the sequence depicted in Figure 7B (which is that of the mature α2M protein).

Finally, the sequence identifiers of previous SEQ ID NOS: 54-57 have been renumbered to SEQ ID NOS: 9-12, which correspond to the amino acid sequences depicted in the amended Figure 3C submitted herewith.

Applicants believe that no new matter has been added by these additions and deletions to the sequence listing.

Amendments to the Figures

Figure 3C has been amended to correctly recite the sequence identifiers for the amino acid sequences depicted in the figure.

Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

I. INFORMATION DISCLOSURE STATEMENT

In the Office Action, the Examiner indicated that the Information Disclosure Statement filed on December 12, 2005 had been acknowledged and considered, and that a signed copy of the Information Disclosure Statement was included with the Office Action (see Office Action, page 2, ¶4). However, the Office Action received by Applicants did not include said signed copy of the Information Disclosure Statement (*i.e.*, the List of References Cited by Applicant ("List") initialed by the Examiner). Applicants have searched the public Patent Application Information Retrieval (PAIR) database, but could not locate the signed copy of the List. Thus, it is respectfully requested that a signed copy of the List be provided to Applicants.

In addition, Applicants point out that a Supplemental Information Disclosure Statement was filed on August 30, 2005. It is respectfully requested that the reference cited in said Supplemental Information Disclosure Statement (*i.e.*, EM) be considered and that a signed copy of the List of References Cited by Applicant accompanying this August 30, 2005 Supplemental Information Disclosure Statement be returned to Applicants.

II. THE OBJECTIONS TO THE SPECIFICATION SHOULD BE WITHDRAWN

The Examiner objected to the disclosure because of certain informalities. First, the Examiner objected to the specification (*e.g.*, page 13, line 16) for improper disclosure of amino acid sequences without a respective sequence identifier.

In response, Applicants note that the specification at page 13, line 16, and at page 59, line 27, was previously amended in Applicants' May 25, 2004 Supplemental Amendment to include the appropriate sequence identifiers, i.e., SEQ ID NO: 6 and 7, respectively. Thus, the objection is obviated and should be withdrawn.

The Examiner also objected to the specification (*e.g.*, pages 15 and 17) because it

contains an embedded hyperlink and/or other form of browser-executable code. In response, Applicants have amended the specification to delete such hyperlink and/or code. Thus, the objection is obviated and should be withdrawn.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

1. The Pending Claims Are Not Anticipated by Bizik

Claims 1, 7-9, 40, 42, and 50 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bizik *et al.* (Int J Cancer. 1986 Jan 15;37(1):81-8, "Bizik *et al.*"). Specifically, the Examiner alleges that the α2M isolated by Bizik *et al.* would, in the absence of evidence to the contrary, comprise α2M-antigenic molecule complexes, wherein the antigenic molecules are those that are over expressed in cancer cells relative to its expression in non-cancerous cells. For the following reasons, Applicants respectfully disagree.

The legal standard for anticipation under 35 U.S.C. § 102 (b) is one of strict identity. In order to anticipate the claimed invention, a single reference must teach each and every element of the claims. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987). In order to establish inherency, "the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999)(quoting *Continental Can Co. v. Monsanto Co.*, 948, F.2d 1264, 1268, (Fed. Cir. 1991)(internal quotations omitted). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* (quoting *Continental Can* at 1749).

Independent claims 1 and 7 relate to a purified molecular complex comprising an α2M polypeptide (which can be α2M or a subsequence thereof) comprising the α2M receptor binding domain noncovalently associated with an antigenic molecule. Independent claims 8 and 9 relate to purified population of molecular complexes which are noncovalent complexes of (i) an α2M, and (ii) an antigenic molecule. Thus, all of the rejected independent claims specify a purified noncovalent complex(es) of α2M (or an α2M polypeptide) and an antigenic molecule.

Bizik *et al.* does not expressly teach purified complexes of α2M noncovalently associated with an antigenic molecule, as specified in claims 1 and 7-9. Bizik *et al.* also does not inherently teach purified complexes of α2M noncovalently associated with an antigenic molecule, for the reasons set forth below.

Bizik *et al.* teaches the isolation of α2M from the conditioned media of cancer cell lines (see Bizik *et al.*, Abstract). In particular, Bizik *et al.* teaches that α2M was purified from conditioned media using a series of steps including ammonium sulfate precipitation followed by size-exclusion chromatography and finally preparative SDS-polyacrylamide gel electrophoresis ("SDS PAGE") followed by electroelution from the relevant gel slice (termed hereinafter, "the First Bizik Procedure") (see Bizik *et al.*, paragraph spanning pages 81 and 82; and Figure 1 on page 82). Bizik *et al.* also teaches the immunoprecipitation of radiolabelled α2M from the conditioned media using rabbit antiserum and fixed protein A-containing staphylococci (termed hereinafter, "the Second Bizik Procedure") (see Bizik *et al.*, paragraph spanning page 82, col. 2 and page 83, col. 1; and Figure 3 on page 84).

Regarding the First Bizik Procedure, Bizik *et al.* does not inherently teach purified complexes of α2M noncovalently associated with an antigenic molecule because the SDS-PAGE purification step used in the First Bizik Procedure would have disrupted any such complexes had they been present. As evidence that the First Bizik Procedure disrupts the noncovalent interaction between α2M and proteins/peptides, Applicants respectfully direct the Examiner's attention to references C01-C03 of the Supplemental Information Disclosure Statement submitted concurrently herewith. Reference C01, *i.e.*, Binder *et al.* (2002), teaches that noncovalent complexes of α2M and peptides are disrupted by treatment for 1 hour with 2% sodium dodecyl sulfate (SDS) or by treatment for 1 hour with 2% SDS and 0.10 M 2-mercaptoethanol (see reference C01, page 2, subsection entitled "Generation of non-covalent alpha2M-peptide complexes" under section entitled "Results"). Reference C02, *i.e.*, Bhattacharjee *et al.* (2000), teaches that dissociation of vascular endothelial growth factor (VEGF) that is noncovalently bound to α2M occurs during SDS gel electrophoresis (see reference C02, paragraph spanning page 26807, col. 2 and page 26808, col. 2). Reference C03, *i.e.*, Birkenmeier *et al.* (1998), teaches that leptin-α2M complexes dissociate by treatment with SDS (see reference C03, page 226, col. 1, first full paragraph; page 227, col. 2, first full paragraph). Together, these references evidence that noncovalent complexes of α2M and proteins/peptides are disrupted by SDS-PAGE. Bizik *et al.* teaches that the samples containing the α2M were heated at 100 °C for 2 minutes in a buffer containing 4% SDS and 10% 2-mercaptoethanol and then subjected to preparative SDS-polyacrylamide gel electrophoresis (see Bizik *et al.*, page 82, col. 1, ¶¶ 1, 2). Thus, the α2M eluted from the preparative SDS-polyacrylamide gel as taught by the First Bizik Procedure would not have contained noncovalently associated peptides because, as evidenced by these references, SDS-

PAGE will disrupt such complexes. Moreover, Bizik itself indicates that the α2M protein purified according to the First Bizik Procedure was "purified to homogeneity," and thus did not contain contaminating peptides or proteins (see Bizik *et al.*, page 83, col. 2, ¶¶ 1 to page 84, col. 2).

In view of the above, Applicants submit that any noncovalent complexes of α2M and antigenic molecules that may have been present in the conditioned media used by Bizik *et al.* would have been disrupted by the First Bizik Procedure and therefore the gel-purified α2M resulting from the First Bizik Procedure did not inherently contain noncovalently complexed proteins or peptides.

Regarding the Second Bizik Procedure, Bizik *et al.* does not inherently teach purified complexes of α2M noncovalently associated with an antigenic molecule because the immunoprecipitated complexes obtained by the Second Bizik Procedure comprise radiolabelled α2M, antibody, and fixed staphylococci bacteria, and thus would not be considered purified. On page 82, col. 2, first full paragraph, of Bizik *et al.*, the Second Bizik Procedure is described. As stated therein, after radiolabelling of the cells and collecting and processing the conditioned medium, "[p]roteins were immunoprecipitated from the conditioned medium according to a standard procedure (Kessler, 1975) using the rabbit antiserum raised against the M_r 140,000 protein and fixed protein A-containing staphylococci (Cowan Strain I; IgG sorb, The Enzyme Center, Malden, MA), as described in more detail elsewhere (Bizik *et al.*, 1985)." The immunoprecipitate was then subjected to SDS-PAGE (see Bizik at p. 85, col. 1, para. 3, and Fig. 6). The SDS-PAGE procedure would disrupt the noncovalent α2M-peptide/protein complexes as discussed above for the First Bizik Procedure. Thus, Applicants' subsequent discussion focuses on the immunoprecipitated complex prior to its being subjected to SDS-PAGE. As quoted above, Bizik cites Bizik *et al.* 1985 *Eur. J. Cancer Clin. Oncol.* 21:317-24 (hereinafter "Bizik 1985") and Kessler 1975 *J. Immunol.* 115:1617-24 (hereinafter, "Kessler") for its immunoprecipitation procedure (see references C05 and C06, respectively, of the Supplemental Information Disclosure Statement submitted herewith).

Bizik 1985 describes radiolabelling and immunoprecipitation (*i.e.*, the Second Bizik Procedure) from conditioned culture media of human sarcoma and melanoma cell lines. Specifically, Bizik 1985 teaches immunoprecipitating the lyophilized radiolabelled proteins by incubating with 2 μl of antiserum and 25 μl of a 10% suspension of *Staphylococcus aureus* (Cowan strain I) as a solid-phase precipitation agent (citing Kessler) before washing and

subjecting to SDS-PAGE (see Bizik 1985, page 318, second paragraph). Kessler teaches a new procedure for the isolation of antibody-bound antigens from cells using protein A-bearing strains of the bacterium *Staphylococcus aureus* (such as Cowan I) in indirect immune precipitations (see Kessler, page 1617, Abstract and col. 2, second full paragraph).

Thus, the complexes obtained by the Second Bizik Procedure comprise radiolabelled α2M, antibody, and the staphylococci bacteria which were used to bind to and precipitate the anti-α2M antibody, as described above (see Bizik 1985 and Kessler, both of which were cited by Bizik *et al.* for its immunoprecipitation procedure). Applicants submit that an α2M preparation containing whole staphylococci bacteria cannot be considered "purified" according to the plain meaning of the word, *i.e.*, to "rid of impurities" and to "rid of foreign or objectionable elements" (see Exhibit 1, page 1111 of the American Heritage College Dictionary, 3rd Edition, 1993).

In addition, the α2M preparation of Bizik *et al.* is not a pharmaceutical composition as recited by claim 1 because it comprises a non-pharmaceutically acceptable component, namely whole staphylococci bacteria, which, moreover, are not a pharmaceutically acceptable carrier.

In summary, Bizik neither expressly nor inherently teaches purified complexes of α2M noncovalently associated with an antigenic molecule as specified in independent claims 1 and 7-9. Accordingly, Bizik *et al.* does not anticipate claims 1, 7-9, or their dependent claims 40, 42 and 50, and Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) over Bizik be withdrawn.

2. <u>The Pending Claims Are Not Anticipated by Fields *et al.*</u>

Claims 43-49 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fields *et al.* (J Virol Methods. 1988 Dec;22(2-3):283-94, "Fields *et al.*"). Specifically, the Examiner alleges that the specification of the instant application teaches that α2M is promiscuous in its ability to bind to proteins, and thus, in the absence of evidence to the contrary, the hepatitis B surface antigen (HBsAg) as purified by Fields *et al.* is complexed to alpha-2-macroglobulin (α2M).

Although Applicants do not agree and in no way acquiesce with the rejection, solely to expedite prosecution and obtain coverage for certain embodiments of the present invention, independent claims 43, 44 and 47 have been amended to recite that the antigen whose antigenicity is displayed by the antigenic molecule of the molecular complex is of an infectious agent other than hepatitis type B virus, and dependent claim 46 has been amended

to delete the recitation of "hepatitis type B virus." Fields *et al.* compares five different purification methods for HBsAg from plasma and indicates that four of the five purification methods result in a purified product contaminated with various plasma proteins including, *inter alia*, α2M (see Fields, Abstract; and page 284, ¶4, lines 10-14). However, Fields *et al.* does not teach the isolation of any antigen other than hepatitis type B virus. Thus, the rejection is obviated and should be withdrawn.

In order to clarify the record, Applicants note that the Examiner has referred to page 3, lines 24-25 of the specification as supporting his statement that α2M is promiscuous in its ability to bind to proteins (see Office Action, page 8). The teaching referred to by the Examiner, quoted in its entirety, is as follows:

> "Alpha (2) macroglobulin promiscuously binds to proteins and peptides with nucleophilic amino acid side chains in a *covalent* manner...[]...and targets them to cells which express the α2M receptor."

See specification, page 3, lines 24-27 (internal citations omitted, emphasis added). Applicants point out that this statement refers to <u>covalent</u> binding to α2M, while claims 43-49 are directed to *noncovalent* complexes of α2M and antigenic molecules.

In summary, Applicants submit that claims 43, 44 and 47, and their dependent claims 45-46 and 48-49, are novel over Fields *et al.*, and respectfully request that the rejection under 35 U.S.C. § 102(b) over Fields be withdrawn.

CONCLUSION

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: August 14, 2006

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Enclosures

ANNOTATED SHEET

8/65

POSITION	MH+	SEQUENCE	
509–518	955.0122	SGFSLGSDGK	(SEQ ID NO: ~~54~~ 9)
328–337	973.1753	GIALDPAMGK	(SEQ ID NO: ~~55~~ 10)
460–469	1152.3010	GGALHIYHQR	(SEQ ID NO: ~~56~~ 11)
338–348	1315.5116	VFFTDYGQIPK	(SEQ ID NO: ~~57~~ 12)

FIG.3C